REMARKS/ARGUMENTS

I. Amendments to the Specification

The specification has been amended to recite subject matter disclosed in prior application no. 09/402,820 ("the '820 application"). The '820 application is incorporated into the instant application by reference in the section entitled "Cross-Reference to Related Applications" that appears on page 1 of the specification. Support for the incorporated subject matter is found in the '820 application at page 8, lines 5-13 and page 10, lines 19-28. Accordingly, the amendments to the specification do not add new matter to the application.

II. Status of the Claims

Upon entry of this Amendment, claims 14, 19, 20, 25, 55, 56, 72, 75, 93-116 and 121-125 are pending.

New claims 121-125 have been added. Support for the new claims is found in the amendments to the specification that are set out on page 2 of this Amendment and are discussed immediately above.

Claims 121-125 are dependent claims that are drawn to one of a method of treating Alzheimer's disease or delaying, inhibiting or suppressing accumulation of amyloid β peptide in patients by administering an antibody that binds amyloid β peptide or a method of delaying, inhibiting or suppressing neurotoxicity of amyloid β peptide by administering an antibody that binds amyloid β peptide. Such methods were identified as invention Groups I and II in a restriction requirement that was issued on July 14, 2004. Following Applicants' election to prosecute invention Group II, the Group I and Group II claims were rejoined for examination in the present application. *See* Office Action mailed February 10, 2005 at page 2. New claims 121-125 are thus directed to the elected invention. Accordingly, new claims 121-125 should be entered and examined in the instant application.

By this Amendment, no new matter has been added to the application.

III. Response to Rejections Under 35 U.S.C. 103(a)

Claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 are rejected as being allegedly obvious over Becker et al., EP 0613 007 ("Becker") in view of Audia et al., U.S. Patent No. 5,965,614. ("Audia") and, alternatively, over Becker, in view of Audia as evidenced by Johnson-Wood, et al., *Proc. Natl. Acad. Sci. USA* (1997) ("Johnson-Wood"). Claims 14, 19, 20, 25, 72, 75, 99-104 and 109-120 are rejected as being allegedly obvious over Becker in view of Mak et al., *Brain Res.*, 1994, 19:138-142 ("Mak").

The rejection is respectfully traversed. To support a finding of obviousness, the Examiner must make basic factual enquires as to (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; and (3) the level of ordinary skill in the pertinent art, and further consider secondary considerations that provide evidence of non-obviousness. *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 406 (2007) ("KSR"), *quoting Graham v. John Deere Co.,* 383 U.S. 1, 17-18 (1966) ("Graham"). *See also Unigene Labs., Inc. v. Apotex,* cv 2010-1006, Fed. Cir. Decided August 25, 2001 (Graham factors are the "factual underpinnings" of obviousness) and MPEP 2141 ("Factual findings made by Office personnel are the necessary underpinnings to establish obviousness.") An obviousness rejection predicated on a combination of prior art references requires that at the time the invention was made there was a rationale or motivation that would have motivated one of ordinary skill in the art to combine the prior art and a reasonable expectation of successfully combining the prior art to arrive at the claimed invention. *In re Dow Chem. Co.,* 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *See also KSR* at 417 (2007) (predictable variation bars patentability) and *In re O'Farrell,* 853 F.2d 894, 903-04 (Fed. Cir. 1988) (requiring reasonable expectation of success).

Here, the Examiner has failed to fairly ascertain the scope and content of the prior art. The Examiner has thus failed to provide the required "factual underpinnings" to sustain the rejection. The Examiner further failed to provide a legitimate motivation or rationale to combine the prior art, and failed to show that there was a reasonable expectation that the prior art could be combined to arrive at the claimed invention. For these reasons, the rejection should be withdrawn.

Applicant has previously responded to the rejections in Amendments filed July 24, 2009 and January 19, 2011, including the respective Declarations filed with the Amendments, which Amendments set forth reasons the rejections should be withdrawn. The aforementioned Amendments and Declarations are incorporated herein by reference. The Applicant thus incorporates the remarks and arguments set forth in the previous responses but for, the sake of brevity and without prejudice or disclaimer, does not repeat them here. Applicant specifically reserves the right to raise all grounds for withdrawal of the rejections in future response, or on appeal.

In further response to the rejections, Applicant submits the accompanying Third Declaration of Kenneth L. Rock Under 37 C.F.R. §1.132 (the "Rock Declaration") that directly refutes both the factual foundation of the rejections and the resulting conclusion that there is a reasonable expectation of success for combining the prior art to arrive at the claimed invention. The rejections should thus be withdrawn because both the factual and legal basis upon which they rely are mistaken.

The factual basis for the rejections is mistaken because it relies on the Examiner's finding that Becker teaches "any" antibody is useful for the treatment of AD. As set forth in the Rock Declaration, the Examiner's finding that Becker teaches "any" antibody is useful for the treatment of AD is not correct. Instead, contrary to the Examiner's finding, one of ordinary skill in the art in April 1997 would have understood that (i) to the extent Becker teaches using anti-Aβ antibodies to treat AD, such teachings are restricted to antibodies that recognize Aβ that is in the β-sheet conformation, and (ii) antibodies that recognize Aβ in "non β-sheet" conformations, i.e.,

Aβ in an α-helical or random coil conformations, would not be useful for treatment of AD. Rock Declaration at paragraph 6.

As set out in the Rock Declaration, a person of ordinary skill in the art in April 1997 thus would have understood that Becker teaches that it is the β-sheet conformer of Aβ that is neurotoxic and is the pathogenic agent in AD, that "non β-sheet" conformers of Aβ are not neurotoxic, and that Becker's teachings reflected the state of the art for AD in April 1997. Rock Declaration at paragraphs 16, 17 and 19. The Rock Declaration further sets out the reasons why a person of ordinary skill in the art in April 1997 would not have reasonably predicted that either of the 3D6 antibody disclosed in Audia and Johnson or the β34-40 antiserum disclosed in Mak would recognize Aβ in a β-sheet conformation. Rock Declaration at paragraphs 29-32. In the absence of such a reasonable prediction, a person of ordinary skill in the art would have had no motivation to use either the 3D6 antibody or the β34-40 antiserum in Mak's disclosed methods.

The Rock Declaration further addresses the differences between how the Examiner construed Becker and how a person of ordinary skill in the art in April 1997 would have construed Becker. Rock Declaration at paragraphs 21-28. As stated by Dr. Rock, the Examiner's assertion that Becker teaches that administration of any Aβ antibody would be useful to treat Alzheimer's disease "is simply wrong." Rock Declaration at paragraphs 20 and 21. As explained by Dr. Rock, Becker's statements that "These antibodies are used in diagnostics, therapeutics or in diagnostic/therapeutic combinations" are ambiguous, both as to the identity of the antibodies to which Becker was referring and as to which antibodies would be useful for which, if any, purpose. Rock Declaration at paragraphs 24-25. Faced with these and other ambiguities in Becker, and when interpreted in the complete context of Becker "in April 1997, a person of ordinary skill in the art would have understood that Becker clearly teaches that only antibodies that recognize Aβ in the β-sheet conformation would be useful to block neurotoxicity and such a skilled person would therefore conclude that it is only such β-sheet reactive antibodies that would be therapeutically useful." Rock Declaration at paragraph 26.

In summary, as set out in detail in the Rock Declaration, the Examiner has failed to make accurate factual findings concerning the scope and content of the prior art, as it would have been understood by a person of ordinary skill in the art in April 1997. The Examiner has failed to provide the "necessary underpinnings" to establish obviousness. For at least this reason, the obviousness rejections should be withdrawn.

The obviousness rejections should also be withdrawn because once the prior art is properly construed it is apparent that there is neither a motivation to combine the prior art to arrive at the claimed invention nor a reasonable expectation that the prior art could be combined successfully. As set out in the Rock Declaration and summarized above, a person of ordinary skill in the art in April 1997 would have construed Becker to teach (at most) that antibodies that recognize Aβ in the β-sheet conformation might be useful for treating AD, but that antibodies that do not recognize Aβ in the β-sheet conformation would not useful for treating AD. Such a skilled person would have also recognized that, based on the information available in April 1997, it was unlikely that the 3D6 monoclonal antibody or the β34-40 antisera would recognize or be specific for Aβ in the β-sheet conformation. In short, person of ordinary skill in the art in April 1997 would have thought that neither the 3D6 antibody nor the β34-40 antiserum possessed the characteristic that Becker teaches is required for an AD therapeutic. It follows logically that there would have been neither a motivation to use the 3D6 antibody or the β34-40 in Becker's methods nor a reasonable expectation that the 3D6 antibody or the β34-40 could be used successfully used in Becker's methods. These are additional reasons why the obviousness rejections should be withdrawn.

As stated by the Supreme Court in KSR, a finding of obviousness requires a showing that "there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR* at 418. An invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* For the reasons set out above and contrary to the Examiner's assertions, in this case, there was no reason to combine the prior art to arrive at the claimed invention. It is the

Applicant and not the prior art that suggests the combination of steps and features called for in the present claims. It is therefore improper for the Examiner to combine elements found in the prior art to arrive at the claimed invention, and the obviousness rejections should be withdrawn.

For all of the reasons set out above, the claims are not obvious over the prior art of record. Reconsideration of the claims and withdrawal of all rejections under 35 U.S.C. §103 is requested.

IV. New Claims

New claims 121-125 have been added. The new claims are written as dependent claims and therefore include all of the features and limitations of at least one of the claims previously presented in the application. Claims 121-125 are thus patentable over the prior art for at least the same reasons set forth above. Claims 121-125 are further believed to comply with all requirements for patentability under §§101 and 112. Allowance of claims 121-125 is requested.

V. Conclusion

This application is in condition for allowance, which is earnestly solicited.

Respectfully submitted,

Date: November 1, 2011

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Daniel G. Chain	Art Unit	: 1649
Serial No.	: 10/084,380	Examiner	: Gregory S. Emch
Filed	: February 28, 2002	Conf. No.	: 3496
Title	: **SPECIFIC ANTIBODIES TO AMYLOID BETA PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHODS OF USE THEREOF**		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

THIRD DECLARATION OF KENNETH L. ROCK, M.D. UNDER 37 C.F.R. §1.132

Kenneth L. Rock declares and states as follow:

1. I am a citizen of the United States, more than twenty-one years of age, and make this Third Declaration in support of the above-identified application (hereinafter "the '380 application").

2. I have previously made two Declarations Under §1.132 in support of the '380 application, a First Declaration that was filed August 29, 2007 and a Second Declaration that was filed on May 19, 2008. The respective contents of my previous Declarations, including my curriculum vitae and details of my background and experience in the field of therapeutic antibodies, are hereby incorporated herein by reference in their entireties.

3. As set forth previously in paragraph 6 of the aforementioned First Declaration, I confirm that I am not a co-inventor of the '380 application and have no financial or business interest in Intellect Neurosciences, Inc., a company that I understand has rights in the '380 application.

4. I have been compensated at my standard consulting rate for my time in preparing this Declaration.

5. I have been asked to report on whether on April 9, 1997 (i.e., the priority date of the '380 application) a person of ordinary skill in the art would have (1) understood the disclosure in Becker et al., European Patent Application No. 0 613 007 ("Becker") to teach that "any" (i.e., all) antibodies that recognize amyloid β protein ("Aβ") would be useful to treat Alzheimer's disease ("AD"), and (2) had a reasonable expectation that certain antibodies disclosed in Audia et al., U.S. Patent No. 5,965,614 ("Audia"), *Johnson-Wood* et al., *Proc. Natl. Acad. Sci. USA*, 1997, 94:1550-1555 ("Johnson-Wood"), and Mak et al., *Brain Res.,* 1994, 19:138-142 ("Mak") would be successful in recognizing Aβ having a β-sheet conformation.

6. For the reasons set forth below, based on my study of Becker, Audia, Johnshon-Wood and Mak, and my knowledge and experience in the fields of therapeutic antibodies and AD, I conclude as follows: (1) On April 9, 1997, a person of ordinary skill in the art would have understood that Becker does not teach that "any" antibodies that recognize Aβ would be useful to treat AD. Upon considering Becker as whole, a person of ordinary skill in the art would, instead, have understood that Becker teaches that antibodies that recognize Aβ that is in the β-sheet conformation would be useful for treatment of AD and that antibodies that recognize Aβ in alternative, "non β-sheet" conformations, i.e., Aβ in an α-helical or random coil conformations, would not be useful for treatment of AD. (2) On April 9, 1997, a person of ordinary skill in the art would not have predicted with any reasonable expectation of success that either of the 3D6 antibody disclosed in Audia and Johnson-Wood or the β34-40 antiserum disclosed in Mak would have recognized Aβ having a β-sheet conformation.

ON APRIL 9, 1997, A PERSON OF ORDINARY SKILL IN THE ART WOULD HAVE UNDERSTOOD THAT BECKER DOES *NOT* TEACH THAT "ANY" ANTIBODIES THAT RECOGNIZE Aβ WOULD BE USEFUL TO TREAT AD

7. Becker first teaches:

> Because senile plaques are invariably surrounded by dystrophic neurites, it was proposed early that β-amyloid peptide is involved in the loss of neuronal cells that occurs in Alzheimer's disease. B.

> Yankner and co-workers were the first to demonstrate that synthetic β-amyloid peptide could be neurotoxic in vitro and in vivo. Other research groups, however, were unable to consistently demonstrate direct toxicity with β-amyloid peptide. Even groups receiving β-amyloid peptide from a common source demonstrate conflicting results.
>
> Becker at column 1, lines 30-46 (internal citations omitted).

Becker thus teaches that, prior to the filing date of the Becker application, Aβ had been identified as a pathogenic agent in AD and that Aβ could be directly toxic for neurons, although not all preparations of Aβ exhibited such neurotoxicity, for reasons that were not clear at the time.

8. Becker performed experiments to measure the neurotoxicity of freshly-prepared and aged Aβ preparations, which had predominantly random coil or secondary β-sheet structure, respectively, and described the following discovery:

> The results of these neurotoxicity experiments demonstrates there is a direct correlation between the degree of β-sheet structure in the β-amyloid peptide and its neurotoxicity. There is minimal neurotoxicity associated with those samples of β-amyloid peptide that have a high degree of random coil in their secondary structure.
>
> Becker at column 5, lines 27-32.

Becker thus purported to discover and disclose that Aβ conformation is a key factor in whether and Aβ causes neurotoxicity and that it is the β-sheet conformation of Aβ that is neurotoxic. Becker's discovery provided a possible explanation as to why different preparations of Aβ varied in possessing or lacking neurotoxicity, i.e., Aβ neurotoxicity depended on whether or not the preparations had Aβ in a β-sheet conformation.

9. Becker does not disclose specific teachings about Aβ having a predominantly α-helical conformation. Becker, however, clearly places Aβ having a predominantly α-helical conformation in the same class as Aβ having random coil conformation. Thus, Becker's

specification makes only five references to Aβ having an α-helical conformation. Each reference is in the context of antibodies that recognize Aβ having an α-helical conformation and in each instance Becker links Aβ having an α-helical conformation with Aβ having a random coil conformation. *See* Becker at column 2, lines 2-4; column 5, lines 47-50; column 7, lines 29-32; and column 7, lines 33-36. In each instance, moreover, Becker distinguishes both the α-helical and random coil conformers from the β-sheet conformer. Becker states, for example:

> In another embodiment of this invention are antibodies which are specific for β-amyloid peptides which have adopted a random coil or α-helix conformation. These antibodies show little binding specificity for β-amyloid peptides which have a great deal of β-sheet conformation.
>
> Becker at column 7, lines 33-38.

Becker thus clearly categorizes Aβ having a random coil or α-helical conformation in a single class that is distinguished from Aβ having a β-sheet conformation.

10. Becker repeatedly reinforces that Aβ in a β-sheet conformation is a pathogenic agent in AD. In describing an assay to identify therapeutics that would block neurotoxicity, for example, Becker states:

> This invention describes a series of assays useful in evaluating the efficacy of agents which inhibit the neurotoxic effects of β-amyloid peptide. These assays employ β-amyloid peptide which is in a predominantly β-sheet conformation. This invention also encompasses antibodies having a specificity for β-amyloid peptide which is predominantly in a β-sheet conformation as well as pharmaceutic formulations containing these antibodies. These antibodies show poor reactivity with β-amyloid peptide which has a great deal of random coil or α-helix secondary structure.
>
> Becker at page 1, Abstract.
>
> This invention depicts assays employing β-amyloid peptide in which the secondary structure of the peptide is predominantly β-sheet.

Becker at column 2, lines 18-20.

> The use, therefore, of β-amyloid peptide which has adopted a predominantly β-sheet conformation allows the development of compounds which specifically inhibit the neurotoxicity.

Becker at column 5, lines 33-37.

11. In April 1997, I was working in the field of therapeutic antibodies and supervising a post-doctoral student in this field. In April 1997, a person of ordinary skill in the art (including by way of example my post-doctoral student) would have recognized that the diagnostic methods set out in Becker's claims also demonstrate that Becker considered Aβ having a β-sheet conformation to be neurotoxic, whereas Aβ in a non β-sheet conformation was not considered to be neurotoxic.

12. Becker's claim 1 reads:

> 1. A method for assaying for agents which inhibit the neurotoxicity of β-amyloid peptide which comprises:
>
> a. causing a sample of purified β-amyloid peptide to adopt a predominantly β-sheet conformation;
>
> b. incubating potential inhibitors of neurotoxicity with the β-amyloid peptide in β-sheet conformation;
>
> c. measuring the neurotoxic properties of each β-amyloid peptide/potential inhibitor mixture; and
>
> d. detecting reduction in the neurotoxicity relative to a control.

13. Becker's claim 3 reads:

> 3. A method for assaying for agents which inhibit the neurotoxicity of β-amyloid peptide which comprises:
>
> a. causing a sample of purified β-amyloid peptide to adopt a predominantly non β-sheet conformation;
>
> b. incubating potential inhibitors of neurotoxicity with the β-amyloid peptide in non β-sheet;

c. manipulating the β-amyloid peptide in such a way that β-amyloid peptide without the potential inhibitor of neurotoxicity adopts a predominantly β-sheet conformation[;]

d. measuring the neurotoxic properties of each β-amyloid peptide/potential inhibitor mixture; and

e. detecting reduction in the neurotoxicity relative to a control.

14. In April 1997, a person of ordinary skill in the art would have understood that Becker's claim 1 identifies potential agents that inhibit the neurotoxicity of Aβ by measuring the ability of such agents to directly reduce the amount of Aβ in the β-sheet conformation. A person of ordinary skill in the art (such as my post-doctoral students) would have recognized this because Becker teaches explicitly that Aβ having a β-sheet conformation is neurotoxic. *See* paragraphs 8-13, *supra*. Thus, the sample of Aβ that has adopted a predominantly β-sheet conformation that is formed in step a would be neurotoxic and the direct binding of a potential inhibitor of Aβ neurotoxicity that is performed in step b would decrease in Aβ by decreasing the amount of Aβ in the β-sheet conformation. This confirms Becker's explicit teaching that Aβ having a β-sheet conformation is neurotoxic.

15. In April 1997, a person of ordinary skill in the art would have understood that Becker's claim 3 (in contrast to claim 1) can identify potential agents that inhibit the neurotoxicity of Aβ by measuring the ability of such agents to inhibit conversion of Aβ having a non β-sheet to Aβ having a β-sheet conformation. Thus, in contrast to claim 1, step a (which calls for causing a sample of purified β-amyloid peptide to adopt a predominantly β-sheet conformation), claim 3, step a calls for causing a sample of purified β-amyloid peptide to adopt a predominantly ***non*** β-sheet conformation. Following addition of a potential inhibitor of Aβ neurotoxicity to the preparation of Aβ in a predominantly non β-sheet conformation (claim 3, step b), claim 3 goes on to include an extra step (relative to claim 1) of manipulating the β-amyloid peptide in such a way that β-amyloid peptide without the potential inhibitor of neurotoxicity adopts a predominantly β-sheet conformation (claim 3, step c). Only after the

extra step has been performed does claim 3 call for determining the neurotoxic properties of the β-amyloid peptide/potential inhibitor mixture, relative to a control.

16. One of ordinary skill in the art in April 1997 would thus have understood that the method of claim 3 confirms that Becker teaches Aβ having a β-sheet conformation is neurotoxic whereas Aβ having any "non β-sheet conformation" (as called for in claim 3) is not neurotoxic.

17. Becker's view (from February 12, 1994) that β sheet conformers of Aβ were neurotoxic whereas non β-sheet conformers of Aβ were not neurotoxic continued to be a prevailing view in the field through the April 9, 1997 filing date of the '380 application. *See* Exhibit A, Cotman, C.W., *Annals NY Acad Sci*, 814:1-16, 1997 Apr 24 ("Cotman") and Exhibit B, Behl, C., *Cell Tissue Res,* 1997, 290:471-480 "(Behl").

18. Cotman, teaches "[t]he common feature of these [i.e., β-amyloid] proteins is the intrinsic property of self-assembling into β-sheet structures and the emergence of various types of pathology" (Cotman at 5), that "aged" β-amyloid spontaneously aggregates and that "*[c]ritically*, β-amyloid peptides that exhibit aggregation demonstrate toxicity in cultured neurons, whereas β-amyloid peptides that do not exhibit an aggregated state do not exhibit toxicity" (Cotman at 5-6, emphasis added) and that "we have observed that assembled, bioactive β-amyloid peptides exhibit β-sheet structure, and that amino acid substitutions that disrupt β-amyloid assembly also prevent β-sheet structure and abolish toxicity" (Cotman at 7) and "it appears that some aspect of β-sheet structure or a related higher-order assembly is necessary" for neurotoxicity (Cotman at 7). Behl teaches that "[r]ecently, it became clear that for Aβ to be toxic, it has to be in an aggregated fibril state" and "proteins within the fibril state are arranged in what is termed cross-β-pleated sheet conformation. This fibril state is a prerequisite for Aβ's toxicity." Behl at 472, internal citations omitted. In agreement with Becker, Cotman and Behl thus teach that Aβ in the β-sheet conformation is neurotoxic, whereas Aβ in non β-sheet conformations is not neurotoxic.

19. In short, based on my background and experience in the field of therapeutic antibodies, in April 1997, a person of ordinary skill in the art would have concluded that Becker unambiguously teaches that Aβ having a β-sheet conformation is neurotoxic, whereas Aβ having a "non β-sheet" conformation is not neurotoxic and Becker's teachings were reflective of the state of the art for AD.

20. Becker teaches that "antibodies of the present invention" are useful for diagnosis and treatment of AD. Becker at column 7, lines 49-52 and column 8, lines 16-18. When taken in the context of Becker considered as a whole in April 1997, a person of ordinary skill in the art would have taken these teachings to mean that antibodies that recognize Aβ having a β-sheet conformation would be useful as therapeutic agents, because such a skilled person would have thought it was the β-sheet conformer that was a neurotoxic agent, whereas Aβ in "non β-sheet" conformations would not have been considered to be neurotoxic. In the absence of "non β-sheet" conformers exhibiting neurotoxicity, one of ordinary skill in the art would have found no rationale in Becker for concluding that antibodies to "non β-sheet" conformers would have any therapeutic effect.

21. I understand that, contrary to my finding that a person of ordinary skill in the art would understand that Becker's teaching that anti-Aβ antibodies may be used as therapeutic agent to treat AD is limited to antibodies that recognize Aβ in the β-sheet conformation, the Examiner of the '380 application takes the position that Becker teaches that "any" anti-Aβ antibody, i.e., including antibodies that do not recognize Aβ in the β-sheet conformation, would be useful as an AD therapeutics. In the latest (May 3, 2011) Office Action for the '380 application, for example, the Examiner asserts, "Becker teaches that administration of any Aβ antibody would be useful to treat Alzheimer's disease." Office Action mailed May 3, 2011 at page 5, lines 17-18.

22. The Examiner's assertion set out in paragraph 20 is simply wrong. Becker discloses no example of administering an antibody to treat AD and includes no explicit statement that "any Aβ antibody would useful to treat Alzheimer's disease."

23. In an Office Action mailed November 12, 2009, the Examiner sets out reasons for concluding that Becker teaches that "any" antibody would be useful for AD therapy. See pages 8-11. The Examiner refers to the text found at Becker, column 7, lines 26-52 and asserts, "Becker describes antibodies to the α-helix conformation of Aβ and in the next sentence states that "these" antibodies are used in therapeutics." Office Action mailed November 12, 2009 at page 8. The Examiner asserts "[t]his is an explicit suggestion to use antibodies to Aβ in the α-helix or random coil conformation for treatment of Alzheimer's disease." *Id.*

24. The Examiner's conclusion that the above-cited passages in Becker are "an explicit suggestion to use antibodies to Aβ in the α-helix or random coil conformation for treatment of Alzheimer's disease" is incorrect. Becker's statement that "These antibodies are used in diagnostics, therapeutics or in diagnostic/therapeutic combinations" (Becker at column 7, lines 39-40) is ambiguous. It is first unclear as to which antibodies Becker was referring, when it says "these antibodies."[1] Additionally, it is unclear as to which, if any, of the alternative uses of a diagnostic or therapeutic any particular one of "these antibodies" may be useful for. In short, Becker does not include an "explicit suggestion" to use antibodies to Aβ in the α-helix or random coil conformation for a particular purpose and, for the reasons set out above, it is my opinion that, in April 1997, a person of ordinary skill in the art would not have concluded that Becker teaches or suggests using antibodies to Aβ in the α-helix or random coil conformation to treat AD.

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[1] The Examiner apparently puts great stock in the fact that the statement "These antibodies are used in diagnostics, therapeutics or in diagnostic/therapeutic combinations" is juxtaposed with a description of antibodies that recognize Aβ in an α-helical or random coil conformation. ("Becker describes antibodies to the α-helix conformation of Aβ and in the next sentence states that "these" antibodies are used in therapeutics.") The statement concerning the different, alternative uses for Aβ antibodies, however, appears in a separate paragraph from the description of antibodies that recognize Aβ in an α-helical or random coil conformation. It is clear, moreover, that the statement concerning alternative uses for Aβ antibodies is directed generally to "antibodies of the invention" and not directed explicitly to antibodies that recognize Aβ in an α-helical or random coil conformation. Becker's statement that "These antibodies are used in diagnostics, therapeutics or in diagnostic/therapeutic combinations" could just as easily refer to (and I believe does refer to) the paragraph that describes antibodies that are specific for Aβ in the β-sheet conformation that is found at column 7, lines 26-32. Contrary to the Examiner's assertion, Becker therefore does not include an "explicit suggestion" that antibodies that recognize Aβ in the α-helix or random coil conformation could be or should be used to treat AD.

25. Becker's statements that, "These antibodies are used in diagnostics, therapeutics or in diagnostic/therapeutic combinations" (Becker at column 7, lines 39-40) and "The antibodies of the present invention are useful in the diagnosis and treatment of mammals suffering from Alzheimer's disease" Becker at column 8, lines 16-18 are similarly ambiguous as to which antibody is useful for what application.

26. In short, Becker's explicit statements say only that collectively (and ambiguously) certain antibodies of the invention can be used in diagnostic or, alternatively, in therapeutic applications. These statements by themselves do not clarify which antibodies (β-sheet versus random coil/alpha helix-specific) are useful for which application. Faced with such ambiguity, a person of ordinary skill in the art must necessarily look at Becker as a whole to understand which antibodies are useful for which use. As set out above, there is no disclosure in Becker that antibodies that are specific for β-amyloid peptide in the random coil or α-helix conformation would be direct therapeutic aids. To the contrary, in April 1997, a person of ordinary skill in the art would have understood that Becker clearly teaches that only antibodies that recognize Aβ in the β-sheet conformation would be useful to block neurotoxicity and such a skilled person would therefore conclude that it is only such β-sheet reactive antibodies that would be therapeutically useful.

27. Additionally, in order for an Aβ specific antibody to be used as a therapeutic agent, it would have to be part of a pharmaceutical composition. Becker discloses pharmaceutical compositions only for β-sheet specific anti-Aβ antibodies:

> This invention also encompasses antibodies having a specificity for amyloid peptide which is predominantly in a β sheet conformation as well as pharmaceutic formulations containing these antibodies. These antibodies show poor reactivity with amyloid peptide which has a great deal of random coil or α-helix secondary structure.
>
> Becker at page 1, Abstract.
>
> This invention also encompasses pharmaceutical formulations comprising an antibody having a specificity for β-amyloid peptide

> which is predominantly in a β -sheet conformation in combination with a parenterally-administrable medium.
>
> Becker at column 2, lines 5-9.

In contrast to Becker's disclosure of pharmaceutical formulations comprising an antibody having a specificity for amyloid peptide which is predominantly in a β sheet conformation, Becker includes no disclosure concerning pharmaceutical compositions comprising antibodies that are specific for the random coil or alpha helical conformation of Aβ. This further demonstrates that Becker only contemplates AD therapy using antibodies that recognize Aβ in the β-sheet conformation.

28. In summary, Becker teaches that only some preparations of Aβ are neurotoxic, that the neurotoxic preparations are only those preparation that contain Aβ having a β-sheet conformation, that inhibiting the β-sheet form of Aβ blocks neurotoxicity, and that only antibodies specific for the β-sheet form are contemplated as pharmaceutical agents. Becker's teachings were reflective of the AD immune-therapeutic field in April 1997. Upon considering Becker's teachings as a whole in April 1997, a person of ordinary skill in the art of AD immune-therapeutics would have concluded that antibodies to Aβ in the β-sheet conformation (and not to other conformations) could be used to treat AD. The Examiner's conclusion that Becker teaches that antibodies to the random coil or α-helix conformation of Aβ would inhibit neurotoxicity and be used to treat AD is not supported by Becker's disclosure and is not consistent with the manner in which Becker's teachings would have been understood by a person of ordinary skill in the art in April 1997.

ON APRIL 9, 1997, A PERSON OF ORDINARY SKILL IN THE ART WOULD *NOT* HAVE PREDICTED WITH ANY REASONABLE EXPECTATION OF SUCCESS THAT EITHER OF THE 3D6 ANTIBODY DISCLOSED IN AUDIA AND JOHNSON-WOOD OR THE β34-40 ANTISERA DISCLOSED IN MAK WOULD HAVE RECOGNIZED Aβ HAVING A β-SHEET CONFORMATION

29. Audia did not define what Aβ conformation was recognized by the 3D6 antibody, nor whether the 3D6 antibody blocks neurotoxicity. Moreover, since 3D6 was raised against and reacts with a short N-terminal peptide of Aβ, a person of ordinary skill in the art would not have expected the 3D6 antibody to react with the β-sheet conformation of Aβ. To determine whether the 3D6 antibody was reactive with the β-sheet specific conformation of Aβ and/or inhibited neurotoxicity would have required additional experimentation. In fact, subsequent characterization of the 3D6 antibody has shown that it detects Aβ in Western blots[2] where the polypeptide would be predicted to be in a random coil, denatured state, indicating that the 3D6 antibody would not recognize Aβ in a β-sheet conformation. A person of ordinary skill in the art in April 1997 reading Audia would thus not have predicted that the 3D6 antibody would recognize Aβ in a β-sheet conformation.

30. Nor did Johnson-Wood define what Aβ conformation is recognized by the 3D6 antibody, or whether the 3D6 antibody blocked neurotoxicity. Johnson-Wood disclosed that the 3D6 antibody bound to amyloid plaques on tissue sections. Johnson-Woods results, however, fail to indicate or suggest that the 3D6 antibody bound to Aβ in the β-sheet conformation. Plaque sections could contain different forms of Aβ, some of which may not be Aβ in the β-sheet form (and, in view of the subsequently discovered ability of 3D6 to bind Aβ on Western blots (*see* paragraph 29) the Aβ by Johnson-Wood was most likely not in a β-sheet conformation) and some of which may not be neurotoxic or associated with AD. A person of ordinary skill in the art in April 1997 reading Johnson-Wood would thus not have predicted that the 3D6 antibody would recognize Aβ in a β-sheet conformation.

31. Mak does not determine whether the β34-40 antisera recognized the β-sheet conformation of Aβ. The fact that the antisera was raised against a short C-terminal peptide, however, would have made it unlikely that this sera recognizes Aβ in the β-sheet conformation.

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[2] *See* Exhibit C, downloaded from website maintained by Alzheimer Research Forum at www.alzforum.org/res/com/ant/default.asp after searching for "3D6 AND Johnson-Wood".

To determine whether β34-40 was specific for the β-sheet specific conformation of Aβ and/or blocked Aβ neurotoxicity would have required additional experimentation.

32. In summary, in April 1997, a person of ordinary skill in the art would have appreciated that the manner in which the 3D6 antibody and β34-40 antiserum were elicited (i.e., with short linear peptides) would have made it unlikely that they would have recognized Aβ in the β-sheet conformation.

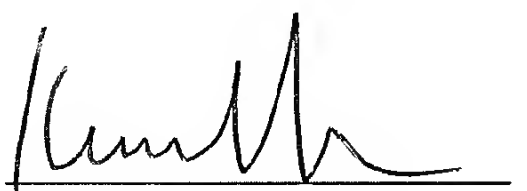
CONCLUSION

33. For the reasons set out above, it is my conclusion that on April 9, 1997, a person of ordinary skill in the art would have understood that Becker does not teach that "any" antibodies that recognize Aβ would be useful to treat AD. Instead, upon considering Becker as whole, a person of ordinary skill in the art would have understood that Becker teaches that antibodies that recognize Aβ that is in the β-sheet conformation would be useful for treatment of AD and that antibodies that recognize Aβ in alternative, "non β-sheet" conformations, i.e., Aβ in an α-helical or random coil conformations, would not be useful for treatment of AD. It is also my conclusion that on April 9, 1997, a person of ordinary skill in the art would not have predicted that either of the 3D6 antibody disclosed in Audia and Johnson-Wood or the β34-40 antiserum disclosed in Mak would have recognized Aβ having a β-sheet conformation.

34. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Declarant's signature:



Kenneth L. Rock, M.D.

10-31-11

Date